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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PORTNER, VIRGINIA ALLEN	
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09/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/598,073	FERNANDEZ-SALAS ET AL.	
	Examiner	Art Unit	
	GINNY PORTNER	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *2,3,9-15 and 23-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,16-22 and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

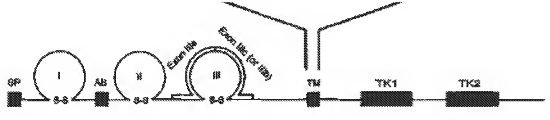
Claims 1-33 are pending; claims 34-78 have been canceled.

Election/Restrictions

1. Applicant's election with traverse of Group I, claim 4, mammalian receptor in the reply filed on June 27, 2008 is acknowledged. Lack of unity of invention exists because the first appearing invention does not make a contribution over the prior art. Applicant's traversal is based on the ground(s) that claims 2-3 are directed towards whether a BoNT/A receptor is transiently or stably contained within a cell, and this aspect does not represent a different general inventive concept because both claims are still within the same inventive concept of detecting BoNT/A activity and do not represent a mammalian receptor different from that of Claim 4.

2. The examiner has not found these arguments persuasive because claims 2 and 3 encompass all of the species of FGFR3 known, and are not limited to mammalian FGFR3 as asserted by Applicant. Claim 4 is not dependent upon either claims 2 or 3, but claim 1; claims 2 and 3 are also directly dependent upon independent claim 1. Applicant's definition encompasses naturally occurring and recombinantly expressed FGFR3 receptors (see instant Specification [0034-0035] from both mammalian and non-mammalian sources.

3. Naturally occurring FGFR3 contains both exogenous (cell surface) as well as endogenous domains :



FGFR3

4. Therefore independent claim 1 encompasses both naturally occurring and recombinantly expressed FGFR3 receptors expressed by any type of cell. Claim 2 reads on a FGFR3 receptor

that is able to move within the cell and is transiently present as an exogenous receptor on the surface of the cell, additionally claim 2 reads on transiently expressed FGFR3 receptors that are recombinantly produced in the cell. Therefore the scope of claims 1 and 2 differ from each other because the cell of claim 2 can be prokaryotic, eukaryotic, mammalian etc and has a FGFR3 receptor that is able to functionally change it's location, albeit, moving into the cell, or being lost from the cell (loss of heterologous DNA used to transform the cell). The Scope of claim 3 reads on receptors that are not lost, but are present in a cell (native cell receptor), or is a receptor present in a recombinant cell that has stable non-native expression of FGFR3 by the cell. Clearly, the presence of heterologous DNA, the variation of the coding sequence of the heterologous DNA, the presence or absence of all functional domains of FGFR3 (see picture able), the location of insertion of the heterologous DNA within a host cell, the vector used to transform the host cell, and the stability of the recombinant host, clearly defines patentably, structurally, functionally distinct species of invention over the various species of naturally occurring cells that express FGFR3. Claims 2-3 will not be rejoined with claim 1 in light of the analysis of the claimed species provided above and in light of Applicant's embodiment described in the instant Specification that provide clear definition of the many types of species encompassed by claims 1, 2 and 3. But upon reconsideration of Applicant's traversal and the teachings of the prior art, the examiner agrees that claims 5-8 should be rejoined with claim 4, as neuronal cells from mammalian sources (human, bovine, mouse and rat) are well known in the art and have been used in methods of detecting BoNT/A activity, and therefore do not constitute undue burden on the examiner. Claims 1, 4-5, 16-22, 28-33 are under consideration.

Applicant's arguments have been fully considered but are not found to be persuasive for the reasons below.

First, the classification system has no statutory recognition whether inventions are independent and distinct. For example, each class and subclass is comprised of numerous completely independent and distinct inventions.

Second, MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term Adistinct≅ is defined to mean that two or more subjects as disclosed are related, for example, as product and method of use, but are capable of separate manufacture, use or sale as claimed, and are patentable over each other (see MPEP 802.1). In the instant situation, the inventions (species) of Groups I are drawn to distinct inventions which are related as separate products capable of separate functions. Restrictions between the inventions are deemed to be proper for the reason previously set forth.

In regard to burden of search and examination, MPEP 803 states that a burden can be shown if the examiner shows either separate classification, different field of search or separate status in the art. Each DNA coding sequence from a different species of animal, the type of vector, or type of cell (prokaryotic, or eukaryotic), the mode of expression (stable or transient) all relative to the claimed methods steps that detect BoNT/A activity constitute structurally, functionally distinct species of invention. In the instant case a burden has been established in showing that the inventions of Groups I-IV are classified separately necessitating different searches of issued US Patents. However, classification of subject matter is merely one indication of the burdensome nature of search. The literature search, particularly relevant in this art, is not co-extensive, because for example a search for a cell vise a search for a specific DNA sequence are clearly different searches, and a search for fish DNA would not necessarily find DNA for a human FGFR3 receptor. Additionally, it is submitted that the inventions of Groups have acquired a separate status in the art. Clearly different searches and issues are involved in the examination of each Group.

For these reasons the restriction requirement is deemed to be proper and is therefore made Final.

Ochiai/Brouwer Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP ∋ 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See AGuidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. ∋ 103(b),≅ 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP ∋ 804.01.

6. The requirement is still deemed proper and is therefore made FINAL. . Claims 1, 4-5, 16-22, 28-33 are under consideration. Claims 2-3, 9-15, and 23-27 stand withdrawn from consideration.

Claim Rejections - 35 USC § 102

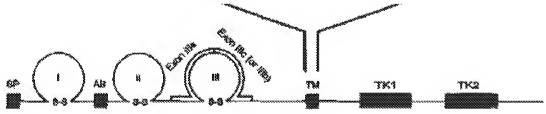
1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Please Note: The following prior art rejections are being made of record in light of the fact that Applicant's definition for FGFR3 receptor includes that wild-type, naturally occurring FGFR3 receptor that is associated with the surface of neuronal cells: Instant Application paragraphs [0034]…… "FGFR3 as a cell surface receptor" and [0035] As used herein, the term "Fibroblast Growth Factor 3 Receptor" is synonymous with "FGFR3" and means a FGFR3 peptide or peptidomimetic which binds BoNT/A in a manner that elicits a BoNT/A intoxication response. FGFR3s useful in the invention encompass, without limitation, **wild type FGFR3s**,

Additionally, the term "exogenous" is being read to include Applicant's wild type species of FGFR3 that is outside the cell membrane, a cell surface receptor that exists at a location that is exogenous to the cell cytoplasm. "TM" is transmembrane, TK1 and TK2 are cytoplasmic kinase domains, I, II and III are exogenous, cell surface domains of FGFR3 known to be present in mammalian neuronal cells.



FGFR3

2. Claims 1, 4, 7, 16-17, 18-19, 22, 28-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Keller et al (1999, reference of record).

3. Keller et al (1999) disclose the instantly claimed invention directed to a method, the method comprising the steps of:

a. **Contacting a sample** (botulinum toxin A obtained from Wako Chemicals, Richmond, VA, the toxin being a preparation/formulation of a purified commercial product, see page 138, section 2.5) to **a cell** that contains an exogenous FGFR3 (cell is a spinal cord (type of neuronal cell) cell culture (mice) that comprises a neuronal component (see page 138, sections 2.3, 2.4, 2.5, 3.1 and Figure 1) the spinal cord cell culture presenting a wild type naturally occurring receptor for botulinum toxin type A which is encompassed by Applicant's definition at Specification [0035]) the exogenous, cell surface receptor binding to BoNT/A complex (see section 2.5, page 138) which resulted in transport of BoNT/A and

b. **Detecting** botulinum toxin type A activity relative to a control cell (Intact SNAP-25, Figure 1, lane 1), wherein the difference in activity (cleavage of SNA-25, lane 2, Figure 1) is indicative of botulinum toxin type A activity (see Figure 1).

While Keller et al does not specifically describe the lectin and protein receptors present in the spinal cell culture for BoNT/A, the spinal cell culture inherently comprised the polysialoganglioside, and a FGFR3 receptor because the botulinum toxin successfully was

translocated across the membrane of the primary cultured spinal cells and cleaved by proteolysis SNAP-25, botulinum toxin type A's substrate (see Figure 1, ledger narrative).

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states AArtisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art≅.

4. Claim 1 and 4 is rejected under 35 U.S.C. 102(e) as being anticipated by Nebrigic (US PG-Pub 2005/0040907 , filing date March 17, 2003, international 371 filing date September 20, 2001, published in English, designated the US) in light of evidence provided by Foodborne Microbial Pathogens,(chapter 8, Clostridium botulinum and Clostridium perfringens, pages 149-164).

5. Nebrigic disclose the instantly claimed invention directed to a method, the method comprising the steps of:

Contacting a sample

[0180] Molecules of interest in the methods described herein may include small molecules, polypeptides, proteins, cyclic polypeptides, peptidomimetics, aptamers, antibodies, scFvs, polysaccharides, receptors, polynucleotides, and/or polynucleotide analogs; and may include therapeutic drugs, pathogens, biological agents, environmental toxins, etc.

[0192] The term "pathogen" as used herein refers to agents that cause disease, including bacteria and viruses.

[0193] The term "biological agent" as used herein refers to one or more molecules obtained from an organism.

[0194] The term "environmental toxin" as used herein refers to one or more molecules that is a poisonous to one or more functions of a cell, and that are present in the terrestrial environment.

to a cell " [0208] Once bound to a sensor array surface, either through specific interaction with affinity agents or by simple use of a sensor array surface as a cell culture substrate, immobilized cells can provide an ordered array for comparison of the biologic responses of various cell types. ..... present on an external surface of a cell. Preferred cell surface components include, but are not limited to, **receptors ……., FGFR3**, ..) that contains an exogenous FGFR3 and

Detecting activity relative to a control cell ([0208]… "cells can provide an ordered array for comparison of the biologic responses"….The attached cells could then be treated with a variety of chemical or biologic agents, and their response monitored.)

While Nebrigic does not specifically describe the sample to contains BoNT/A, the reference does disclose environmental samples for the detection of environmental toxins (see [0180 and 0194], and in light of evidence provided by Foodborne Microbial Pathogens that describes Clostridium botulinum toxins to be encountered/contained in environmental samples (see page 149, last paragraph "grows in animal intestines and spores are found in soil and plants") , Nebrigic inherently anticipates the instantly claimed invention as now claimed in light of the activity that is detected is generically claimed in independent claim 1, and Nebrigic detects a difference in the biological activity due to the presence of environmental toxins present in samples, the activity detected when contacted with cells that express FGFR3.

Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states AArtisans of ordinary skill may not recognize

the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art≅.

Please Note: The following prior art rejection is being made of record in light of the fact that Applicant's definition for FGFR3 receptor includes that wild-type, naturally occuring FGFR3 receptor that is associated with the surface of neuronal cells: Instant Application paragraphs [0034]..... "FGFR3 as a cell surface receptor" and [0035] As used herein, the term "Fibroblast Growth Factor 3 Receptor" is synonymous with "FGFR3" and means a FGFR3 peptide or peptidomimetic which binds BoNT/A in a manner that elicits a BoNT/A intoxication response. FGFR3s useful in the invention encompass, without limitation, **wild type FGFR3s**,

Additionally, the term "exogenous" is being read to include Applicant's wild type species of FGFR3 that is outside the cell membrane, a cell surface receptor that exists at a location that is exogenous to the cell cytoplasm

6. Claims 1, 18, 28-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Steward et al (1 common inventor, Aoki, and common Assignee, Allergan, US Pat.7,208,285).

7. Steward et al disclose and claim a method of detecting BoNT/A activity in a sample, the method comprising the steps of:

Contacting a cell (see Steward et al, claims 27, 50 and 82 "said contacted cell"; Brief Summary test, paragraph 4 "clostridial neurotoxins are highly potent and specific poisons of neural **cells,**")

with a sample

(see Steward et al claims 4-8 and Description paragraphs 137-138 the term sample means... includes term

"sample" means any biological matter that contains or potentially contains an active clostridial toxin, or light chain or proteolytically active fragment thereof. Thus, the term

sample encompasses but is not limited to purified or partially purified clostridial toxin; **recombinant** single chain or dichain toxin with a naturally or non-naturally occurring sequence; chimeric toxin containing structural elements from multiple clostridial toxin species or subtypes; **recombinant** toxin light chain with a naturally occurring or non-naturally occurring sequence; bulk toxin; formulated product; cells or crude, fractionated or partially purified cell lysates, for example, engineered to include a **recombinant** nucleic acid encoding a clostridial toxin or light chain thereof, including bacterial, baculoviral and yeast lysates; raw, cooked, partially cooked or processed foods; beverages; animal feed; soil samples; water samples; pond sediments; lotions; cosmetics; and clinical formulations. It further is understood that the term sample includes tissue samples, including, without limitation, mammalian samples, primate samples and human samples, and encompassing samples such as **intestinal samples**, for example, infant intestinal samples, and samples obtained from a wound. Thus, it is understood that a method of the invention can be useful, without limitation, to assay for clostridial toxin protease activity in a food or beverage sample; to assay a sample from a human or animal, for example, exposed to a clostridial toxin or having one or more symptoms of a clostridial toxin; to follow activity during production and purification of clostridial toxin, and to assay formulated clostridial toxin products, including pharmaceuticals and cosmetics."), and

c. **Detecting** a difference in BoNT/A activity of said contacted cells (treated cell substrate) as compared to a control cell (see control substrate in the cell).

Steward et al inherently anticipates the instantly claimed invention as now claimed. The applied reference has a common inventor and assigenee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Please Note: The following prior art rejection is being made of record in light of the fact that Applicant's definition for FGFR3 receptor includes that wild-type, naturally occuring FGFR3 receptor that is associated with the surface of neuronal cells: Instant Application paragraphs [0034]…… "FGFR3 as a cell surface receptor" and [0035] As used herein, the term "Fibroblast Growth Factor 3 Receptor" is synonymous with "FGFR3" and means a FGFR3 peptide or peptidomimetic which binds BoNT/A in a manner that elicits a BoNT/A intoxication response. FGFR3s useful in the invention encompass, without limitation, **wild type FGFR3s**,

Additionally, the term "exogenous" is being read to include Applicant's wild type species of FGFR3 that is outside the cell membrane, a cell surface receptor that exists at a location that is exogenous to the cell cytoplasm

8. Claims 1,4-8,16-22, 28-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Fernandez-Salas et al (US Patent 7,183,066)

Fernandez-Salas et al disclose and claim the instantly claimed invention directed to a method that comprises the steps of:

Contacting a sample

"sample" means any biological matter that contains or potentially contains an active clostridial toxin. Thus, the term sample encompasses but is not limited to purified or partially purified clostridial toxin; recombinant single chain or dichain toxin with a naturally or non-naturally occurring sequence; recombinant clostridial toxin with a modified protease specificity; recombinant clostridial toxin with an altered cell specificity; chimeric toxin containing structural elements from multiple clostridial toxin species or subtypes; bulk toxin; formulated product; cells or crude, fractionated or partially purified cell lysates, for example, engineered to include a recombinant nucleic acid encoding a clostridial toxin; bacterial, baculoviral and yeast lysates; raw, cooked, partially cooked or processed foods; beverages; animal feed; soil samples; water samples; pond sediments; lotions; cosmetics; and clinical formulations. It further is understood that the term sample encompasses tissue

samples, including, without limitation, mammalian tissue samples, livestock tissue samples such as sheep, cow and pig tissue samples; primate tissue samples; and human tissue samples. Such samples encompass, without limitation, intestinal samples such as infant intestinal samples, and tissue samples obtained from a wound."

To a cell

"The term "cell," as used herein, means any eukaryotic cell that expresses,…….at least one receptor that binds a clostridial toxin. The term cell encompasses, without limitation, primary cells; cultured cells; established cells; normal cells; transformed cells; tumor cells;....cells of a variety of species and cell types. Thus, the term cell encompasses, without limitation, mammalian cells such as murine, rat, ….. bovine, ….and human cells. A variety of cells are useful in the invention including, without limitation, primary cells; established cells; human cells; neuronal cells such as primary neurons, established neurons and human neurons

A variety of cells are useful in the invention including, without limitation, primary cells; established cells; human cells; neuronal cells such as primary neurons, established neurons and human neurons; and non-neuronal cells, which can be, for example, glandular cells such as pancreatic acinar cells. Neurons useful in the invention include CNS neurons and peripheral neurons; as non-limiting examples, such neurons include neuroblastoma cells, spinal cord neurons, dorsal root ganglion neurons, cerebral cortex neurons, cerebellar neurons, hippocampal neurons and motor neurons.

A neuron useful in the invention can be a peripheral neuron or CNS neuron; as non-limiting examples, spinal cord neurons such as an embryonic spinal cord neurons, dorsal root ganglia (DRG) neurons, cerebral cortex neurons, cerebellar neurons, hippocampal neurons and motor neurons can be useful in the invention as described further below.

Exemplary neurons useful in the invention include, but are not limited to, primary cultures of embryonic DRG neurons, for example, primary cultures of embryonic rat DRG neurons as described in Welch et al., Toxicon 38:245 258 (2000); and primary cultures of fetal spinal cord neurons, for example, primary cultures of murine fetal spinal cord neurons as described in Neale et al., J. Cell Biol. 147:1249 1260 (1999), or Chaddock et al., Infect. Immun. 68:2587 2593 (2000)).

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Exemplary neuronal cell lines useful in the invention include, without limitation, neuroblastoma cell lines such as LA-N-2, SH-SY5Y, N2a, NS-20Y and NIE-115; hybrid cell lines, including neuroblastoma/glioma hybrids such as NG108-C15; motor neuron cell lines such as NSC-34 and NSC-19; spinal cord cell lines such as M4b; CNS cell lines; cerebral cortex cell lines such as CNh; dorsal root ganglion cell lines such as G4b; hippocampal cell lines such as HT-22; and pheochromocytoma cell lines such as PC12.

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A neuronal cell line useful in the invention can be, for example, a neuroblastoma cell line such as a murine, primate or human neuroblastoma cell line. Exemplary neuroblastoma cell lines useful in the invention include, without limitation, LA-N-2, SH-SY5Y, N2a, NS-20Y and NIE-115. As an example, the invention can be practiced with the LA-N-2 human neuroblastoma cell line, which has properties of cholinergic neurons and expresses well characterized cholinergic markers (Rylett et al., J. Neurochem. 61:1388 1397 (1993); Singh et al., J. Neurosci. Res. 25:476 485 (1990); and Yeh et al., Neuroscience 27:309 315 (1988)). As a further example, the invention can be practiced with the SH-SY5Y human neuroblastoma cell line, which exhibits inhibition of [.sup.3H]-noradrenaline release induced by K.sup.+/Ca.sup.2+ upon exposure to botulinum toxin (Purkiss et al., Neurotoxicology 22:447 453 (2001)).

And detecting the presence of BoNT/A activity of the contacted cell relative to a control cell ([101] the contacted cell as compared to the control cell is indicative of clostridial toxin activity.)

While Fernandez-Salas et al does not specifically describe the lectin and protein receptors present in the cell for BoNT/A (see claim 8, "BoNT/A"), the cell inherently comprises a polysialoganglioside, and a FGFR3 receptor because the botulinum toxin is able to translocate

across the membrane and evidence protease activity (see Fernandez-Salas et al, claim 1, paragraph (c), col. 119, lines 44-46).

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states AArtisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

9. The applied reference has a common Fernandez-Salas, and Aoki are common inventors, (Garay is not listed on this applied reference/patent but is an inventor on the instant Application) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 4-8, 16-22, 28-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-9, 28-32, 39 of U.S. Patent No7,183,066 (also known as US PG-pub2004/0072270). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed genus of method of detecting BoNT/A activity is broader in scope that the allowed species, which is encompassed by the instantly claimed genus based upon the disclosure in the instant Specification at paragraph [0092] Assays that detect the cleavage of a BoNT/A substrate after exposure to BoNT/A can also be used to assess for the presence of BoNT/A activity. In these assays, generation of a BoNT/A cleavage-product would be detected after BoNT/A treatment. As a non-limiting example the SNAP-25 cleavage assay disclosed in the present specification can detect the cleavage of a BoNT/A substrate after exposure to BoNT/A and thereby be useful in assessing BoNT/A activity

(see Example I). Other non-limiting methods useful to detect the cleavage of a BoNT/A substrate after exposure to BoNT/A are described in, e.g., Lance E. Steward et al., FRET Protease Assays for Botulinum Serotype A/E Toxins, U.S. Patent Publication No. **2003/0143650 (Jul. 31, 2003)**; and Ester Fernandez-Salas et al., Cell-based Fluorescence Resonance Energy Transfer (FRET) Assays for Clostridial Toxins, U.S. Patent Publication **2004/0072270 (Apr. 15, 2004).** It is understood that these and similar assays for BoNT/A substrate cleavage can be useful in assessing BoNT/A activity.

12. The allowed species anticipates the instantly claimed genus as now claimed. The instantly claimed invention is obviated by the allowed species of US Pat. 7,183,066.

13. Claims 1, 18, 28-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-8, 27, 29, 31-35,50, 58,66-67,69-771,84 of U.S. Patent No. 7,208,285 (also known as US PG-pub2003/0143650). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed genus of method of detecting BoNT/A activity is broader in scope that the allowed species, which is encompassed by the instantly claimed genus based upon the disclosure in the instant Specification at paragraph [0092] Assays that detect the cleavage of a BoNT/A substrate after exposure to BoNT/A can also be used to assess for the presence of BoNT/A activity. In these assays, generation of a BoNT/A cleavage-product would be detected after BoNT/A treatment. As a non-limiting example the SNAP-25 cleavage assay disclosed in the present specification can detect the cleavage of a BoNT/A substrate after exposure to BoNT/A and thereby be useful in assessing BoNT/A activity (see Example I). Other non-limiting methods

useful to detect the cleavage of a BoNT/A substrate after exposure to BoNT/A are described in, e.g., Lance E. Steward et al., FRET Protease Assays for Botulinum Serotype A/E Toxins, U.S. Patent Publication No. **2003/0143650 (Jul. 31, 2003)**; and Ester Fernandez-Salas et al., Cell-based Fluorescence Resonance Energy Transfer (FRET) Assays for Clostridial Toxins, U.S. Patent Publication **2004/0072270 (Apr. 15, 2004).** It is understood that these and similar assays for BoNT/A substrate cleavage can be useful in assessing BoNT/A activity.

14. The allowed species anticipates the instantly claimed genus as now claimed. The instantly claimed invention is obviated by the allowed species of US Pat. 7,208,285

Conclusion

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Various references have been cited to show assays for detecting botulinum toxin activity.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ginny Portner/
Examiner, Art Unit 1645
September 11, 2008

/Mark Navarro/
Primary Examiner, Art Unit 1645